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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,068	09/05/2003	Robert J. Levy	CHOP.0100.1	8339

110 7590 02/07/2007

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,068	LEVY ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2006 and 01 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,41-45,52-60 and 66-70* is/are pending in the application.

4a) Of the above claim(s) *67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,41-45,52-60,66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20061201*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claim 60 drawn in part to an invention nonelected with traverse in the reply filed 3/8/06 A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim 67 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/8/06. Claim 67 depends form claim 37, which has been canceled. Claim 37 was directed to a non-elected invention, and withdrawn from examination. Claim 67 is presumably directed to the same non-elected invention.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/851,327, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Claim 53 is directed to a composition for enhancing efficiency of delivery of a nucleic acid to a "vascular smooth muscle cell." The only place in the '327 specification mentioning "vascular smooth muscle cells" (page 24, lines 1-4) is a discussion of the function of tenascin C produced in vascular smooth muscle cells, and does not describe using an "agent" to enhance transfection of vascular smooth muscle cells. Examples 1-3 describe transfecting A10 cells, an immortalized cell line derived from rat arterial smooth muscle cells, but does not teach that vascular smooth muscle cells in general are intended targets of the method.

Applicant's arguments filed 7/25/06 have been fully considered but they are not persuasive. Page 23, line 29, to page 24, line 4, simply discusses what was known about which cells Tenascin C was expressed in and its biological functions in vascular smooth muscle cells. It does not describe the invention as being directed to transfection of vascular smooth muscle cells. Furthermore, this teaching in the specification would at least raise doubts in one of skill in the art that further induction of Tenascin C expression would even be necessary, rather than be viewed as a teaching that transfection of generic VSMCs, specifically, was contemplated as part of the invention. A10 cells (Example 1) are derived from rat arterial smooth muscle cells, and may or

may not be viewed as being arterial smooth muscle cells. It remains that the '327 disclosure provides no explicit indication that transfection of VSMCs, in general, was contemplated as an embodiment of the invention.

In addition, a reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. The instant application was filed as a division of the '327 application. For the reasons set forth above, the subject matter of instant original claim 53 is not supported in the '327 application. Consequently, the instant application is a continuation-in-part of the '327 application, not a division.

To rectify this discrepancy, Applicant is required to either a) amend the first sentence of the specification, which was amended in the amendment filed 7/25/06, to indicate the instant application is continuation-in-part of the '327 application; or b) cancel claim 53, in which case the application would properly be a division of the '327 application. Failure to take appropriate action in the reply to the instant Office action to rectify this discrepancy will be considered to be non-responsive to this Office action. Whichever option is chosen, it must be consistent with the option chosen to address the objection to the specification set forth below.

Oath/Declaration

The oath or declaration remains defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 602.

The instant application was filed with a preliminary amendment, but without an executed oath or declaration. The later filed declaration fails to properly identify the application as having been amended on 9/5/03 (see line 8 of the declaration filed 5/13/04). Applicant is required to provide a substitute declaration that identifies the amended application to which it applies by indicating the date the amendment was filed. Also see 37 CFR 1.63 (b)(2).

Applicant's arguments filed 7/25/06 have been fully considered but they are not persuasive for the reasons set forth above.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required. The specification does not describe using the claimed composition to transfect a "vascular smooth muscle cell" (claim 53). This may be corrected either a) by amending the specification to provide proper antecedent basis for the claimed subject matter, or b) by canceling claim 53. Whichever remedy is chosen, it must be consistent with the remedy

chosen to correct the relationship between this application and the '327 application as set forth above.

Claim Objections

Claim 60 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 60 recites that the agent is selected from a group of agents that includes denatured collagen, a peptide of denatured collagen and several other non-elected agents. Claim 59, from which claim 60 depends, recites that the agent is denatured collagen or a peptide of denatured collagen. Consequently, claim 60 goes beyond the scope of the claim from which it depends with respect to the agent.

Claim 60 remains objected to because of the following informalities: these claims embrace non-elected inventions. Appropriate correction is required prior to allowance.

Claim Rejections - 35 USC § 112

Claims 68-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 68-70 are directed to embodiments wherein the collagen is denatured at 100°C at pH 3. Applicant points to page 28, lines 10-11. However, here the specification teaches that the collagen is held under these conditions for 1 hour specifically, not for just any unspecified period time period as permitted by the claims. Furthermore, these conditions are used to denature type I collagen (bovine) specifically. The specification does not teach that these conditions may be or should be generally employed for other types of collagen, e.g. types II, III, IV, etc. Consequently, the limitation in these claims is broader than that originally disclosed due to the omission of the other features of the collagen denaturation as originally described, and thus constitutes impermissible new matter.

Claims 34 and 41-44 remain rejected and claim 68 is rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 4/21/06, because the specification, while being enabling for enhancing transfection of cultured cells with cationic liposomes comprising plasmid by growth in the presence of tenascin C or denatured collagen before, during, or after transfection or cytochalasin D after transfection, does not reasonably provide enablement for any other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 57 and 58 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record set forth in the Office action

of 4/21/06. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The compositions of these claims include limitations taught in the specification only as being for *in vivo* use.

Applicant's arguments filed 7/25/06 have been fully considered but they are not persuasive. The amendment to the claims overcomes the original rejection in part, specifically as directed to agents other than denatured collagen or a peptide thereof. The grounds of rejection set forth on pages 10 and 11 of the 4/21/06 Office action remain.

Applicant points to Perlstein et al. as evidence of using the claimed invention *in vivo* where a stent coated with a composition containing denatured collagen and nucleic acid is used to transfect cells, and points to the specification teaching that the agent and/or nucleic acid can be delivered using a stent (page 18), or contained within a controlled release film (page 16). In response, Perlstein was published Aug. 2003, over three years later than the effective filing date of the instant application. Consequently, it does not provide evidence of the state of the art at the time the instant invention was originally made. Indeed, Perlstein (page 1424, bottom col. 2) states: "[A]t this time, no other researchers have reported results with plasmid DNA delivery stents."

Furthermore, Applicant fails to indicate where the specification teaches transfection of arterial cells *in vivo* using a stent, much less for any practical purpose, or that the stent should be coated with denatured collagen containing the plasmid, then treated with carbodiimide to crosslink the collagen, then coated with polylactic-polyglycolic acid (PLGA) as described in Perlstein (paragraph bridging paragraphs 1-2, page 1423), nor could the examiner find any such

guidance. Furthermore, Perlstein teaches that coating only with the denatured collagen-DNA composition was not suitable for *in vivo* use and that the cross-linking and outer coating of PLGA was necessary. Nowhere does the specification direct one to this particular stent preparation. Perlstein shows that inventive activity would have been required in order to practice the invention just for this one potential embodiment of the claimed invention. Also, Applicant fails to explain how transfection with a plasmid that encodes GFP constitutes a practical use of the claimed invention that would satisfy 35 USC 101. Rather, the experiments described in Perlstein demonstrate using the claimed invention as an object of further research to determine how to achieve a useful result with the method, which would not satisfy the utility requirement.

In addition, the single embodiment illustrated in Perlstein is not commensurate in scope with the claims, which embrace transfecting any type of cell, e.g. neurons, muscle cells, epidermal cells, etc., or in any tissue, e.g. brain, muscle, bladder, etc. with nucleic acid encoding any gene product, using any type of vector, e.g. plasmid, viral vector, or linear nucleic acid, etc., for any conceivable purpose, e.g. treating Alzheimer's disease, hemophilia, Gaucher's disease, macular degeneration, etc.

The law under §112, first para. requires that the disclosure in the application shall inform those skilled in the art how to use the invention, not how to find out for themselves how to use it. *In re Gardner*, 166 USPQ 138, 141 (CCPA 1970). The invention is directed to the highly unpredictable subject area of gene therapy. The instant application simply tosses out the idea that the instant invention might be used *in vivo*, but fails to disclose how it could be used for any practical purpose or used effectively for any practical purpose *in vivo*.

Claim Rejections - 35 USC § 102

Claims 34, 41-45, 52, 53, 55, 59, 60, and 66 remain rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Arrow et al., US 5,849,902 for the reasons of record set forth in the Office action of 4/21/06. Claim 52 was inadvertently omitted from the rejection in the preceding Office action, which should have indicated that claims ..., 51-53, ... were rejected, rather than claims ..., 51, 53, ... It was evident that claim 52 should have been included in the rejection since the grounds of rejection indicated that the nucleic acid was a plasmid, and claim 60, which is directed to a kit containing the composition recited in claim 52, was rejected.

Claims 34, 41, 44-45, 52-56, 58-60, and 66 remain rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Isner, US 5,652,225 for the reasons of record set forth in the Office action of 4/21/06.

Claims 34, 41, 44, 45, 52-54, 56, 59, 60, and 66 remain rejected under 35 U.S.C. 102(a) & (e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Truong et al., US 6,025,337 for the reasons of record set forth in the Office action of 4/21/06.

Applicant's arguments filed 7/25/06 have been fully considered but they are not persuasive. Applicant argues that since the cited prior art fails to teach that the gelatin used in the prior art methods enhanced cytoskeletal permissiveness for transfection and consequently transfection, it does not anticipate the claimed invention. In response, the claims contain no

physical limitations on either the materials used or the actions taken that distinguish the claimed invention from that in the prior art. If the method is the same then the result must be the same, and whether those in the prior art were aware that the gelatin they were using had this additional advantage or property does not preclude anticipation. See MPEP 2112, 2112.01, 2112.02.

The examiner was unable to locate a copy of *Tilghman v. Proctor* (1881). The instant situation is not the same as that in the remaining court cases relied upon by Applicant. In *Rappaport v. Demont* the key limitation was not only that the compound was used to treat a specific condition but that the compound was administered at a particular time (at the hour of sleep) to treat that particular condition. In *In re Marshall*, the distinguishing feature was the required dosage of the compound, which was contraindicated by prior art cited in the rejection. In other words, the claims in question recited material limitations that limited the actions or the materials used in the method that were not found in the prior art or in the interfering application. In contrast, the claims here are directed to treating any cell, including those described in the prior art, with gelatin and nucleic acid, as in the prior art; and the goal of the claimed and prior art methods, i.e. transfection of cells, is the same.

Applicant does not argue or present evidence that the methods described in the prior art would not involve enhancing transfection due to contacting the cells with the gelatin, and certainly not that prior knowledge of the effect was necessary in order for it to occur. Rather Applicant's argument appears to turn on whether those in the prior art were aware of this feature of the methods they disclose. Based on Applicant's reasoning, the question of whether one were practicing the claimed invention or not would depend on whether the practitioner was aware that contacting target cells with gelatin before, during, or after contacting with nucleic acid would

increase transfection. If unaware, then one would not be practicing the invention, but if aware then one would be practicing the invention. This is clearly an untenable position.

Regarding claims 68-70, Applicant's comments, filed 12/1/06 in response to the request for information of 9/26/06, regarding the Jones (1999) publication are acknowledged. In addition, Jones is the only prior art that the Examiner is aware of that teaches denaturing collagen near pH 3 at 100°C or near to using 0.17% acetic acid (28mM) at 100°C. Jones used 20 mM acetic acid, which would yield a pH of about pH 3.25. The Examiner found a wide variety of different conditions in use to denature collagen to make gelatin that result in gelatin of differing physical properties, but no evidence that the particular conditions recited in claims 68-70 (or in Jones) were commonly (or even uncommonly) used. Consequently, there is no evidence of record that suggests preparing the denatured collagen for use in the methods or compositions of Arrow, Isner, or Truong under the conditions recited in claims 68-70, or that the gelatin would be physically identical to that prepared by other prior art methods. If the recited method results in gelatin that also has different functional properties with respect to transfection, then all the claims should be limited to the method of preparing the gelatin recited in claims 68-70. However, there is no indication in the specification that enhancement of transfection requires or depends upon the recited conditions for preparing the gelatin.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
Art Unit 1633